Maternal genetic variation in inflammatory response genes interact with a measure of air pollution exposure to influence birthweight in non-Hispanic black women

AE Ashley-Koch[1], ME Garrett[1], KS Quinn[1], AC Buskwofie[1], KS Soldano[1], S Edwards[2], GK Swamy[3], ML Miranda[2,4]

[1]Center for Human Genetics, Duke University Medical Center, [2]Nicholas School of the Environment, Duke University, [3]Department of Obstetrics and Gynecology, Duke University Medical Center, [4]Department of Pediatrics, Duke University Medical Center, Durham, NC

INTRODUCTION

- African American women are at higher risk for adverse birth outcomes than Caucasian women, even after controlling for social and demographic differences (Martin et al, 2010; Behrman et al, 2007; Johnston et al, 2001; Wise et al, 1985).
- Inflammation contributes to adverse birth outcomes such as low birthweight (BWT), preterm birth (PTB) and small for gestational age (SGA).
- Both maternal and cord blood levels of inflammatory proteins have been previously associated with infant BWT, PTB, and SGA (Lowe et al, 2010; Amarilyo et al, 2011; Neta et al, 2010).
- Variability in maternal inflammatory response may be exacerbated by environmental exposures during pregnancy such as particulate air pollution, which has been shown to influence risk of low BWT, PTB, fetal growth restriction, and fetal and infant death (e.g. Gray et al., 2010; Xu et al., 2011).
- We therefore examined how variation in maternal inflammatory genes interacts with residential distance to the nearest major roadway to affect infant BWT among non-Hispanic black (NHB) women in the Healthy Pregnancy, Healthy Baby study.

STUDY DESIGN

- The Healthy Pregnancy, Healthy Baby Study is a prospective cohort of pregnant women aimed at identifying genetic, social, and environmental contributors to racial disparities in pregnancy outcomes among women in the US South.
- Beginning in July 2005, pregnant women with a singleton gestation at less than 28 weeks, without congenital anomalies, who were English-literate and lived within Durham County, NC were recruited from the Duke University Obstetrics Clinic and the Durham County Health Department Prenatal Clinic at the Lincoln Community Health Center.
- Psychosocial and socioeconomic factors were assessed via self-completed survey during pregnancy.
- Maternal blood samples were collected for candidate gene analysis and gene-environment interactions.
- Electronic medical records were reviewed for pre-existing conditions, pregnancy complications, and birth outcomes.
- Maternal residential address at enrollment was georeferenced and the distance to the nearest major roadway was calculated as a proxy for exposure to traffic-related air pollution.
- 673 NHB women had delivered their pregnancies and had genetic data available for analysis.

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GENOTYPING

- LD Select was used to identify 'haplotype tagging' SNPs to minimize repetitive data coming from SNPs within the same haplotype block.
- SNP genotyping was performed by TaqMan, using 'Assays-On-Demand' or 'Assays-By-Design' SNP genotyping products (Applied Biosystems, Foster City, CA).
- For quality control, blinded duplicate and CEPH samples were included on all DNA plates and were required to match 100%. Further, the genotypes of at least 95% of the samples had to be called with certainty to be considered for statistical analysis.

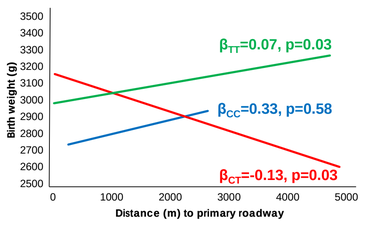
STATISTICAL ANALYSIS

- Deviations from Hardy-Weinberg equilibrium (HWE) were tested using the Genetic Data Analysis program.
- Analysis of Variance (PROC GLM, SAS System V9) was used to evaluate the association between maternal genotype and infant BWT, as well as potential interactions between htSNPs and roadway proximity.
- 105 independent, haplotype tagging SNPs in 20 inflammatory pathway candidate genes were tested.
- Because African Americans are an admixed population, we used the Illumina African American admixture panel to investigate possible sub-structure within our NHB population. Genome-wide percent European ancestry for each NHB woman was estimated using the linkage model in STRUCTURE (Falush et al, 2003).
- Several covariates were included in the analysis:
  - Maternal age (18-20 yrs, 21-34 yrs, ≥ 35 yrs)
  - Infant sex
  - Maternal report of tobacco use (yes, no, quit)
  - Maternal education (high school vs. any secondary education)
  - Insurance status (private vs. not private)
  - Parity (first born vs. other)
  - Estimate of European ancestry

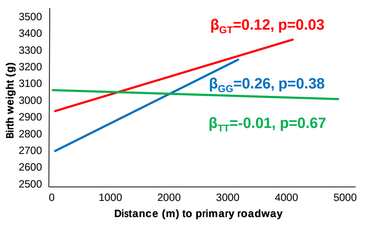
RESULTS

- Mean infant BWT was 3034 grams with mean gestational age of 268.8 days.
- 4 SNPs deviated from HWE (rs2243253 in *IL4*, p=0.009; rs2243123 in *IL12A*, p=0.012; rs1571344 in *CR1*, p=0.005; and rs2069714 in *INFG*, p=0.035).
- 7 SNPs provided nominal evidence for main effects on infant BWT:
  - rs17047661 in *CR1* (p=0.006)
  - rs1518111 in *IL10* (p=0.008)
  - rs2227538 and rs2227306 in *IL8* (p=0.01 and 0.02, respectively)
  - rs2853694 in *IL12B* (p=0.03)
  - rs2069840 in *IL6* (p=0.03)
  - rs568408 in *IL12A* (p=0.04)
- 5 SNPs interacted with roadway proximity to influence infant BWT:
  - 2 SNPs in *TLR4*

rs12344353 (p=0.01)

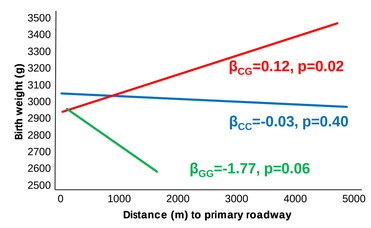


rs5030725 (p=0.03)

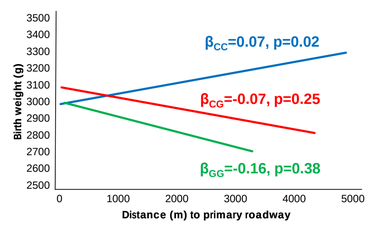


  - 2 SNPs in *IL4*

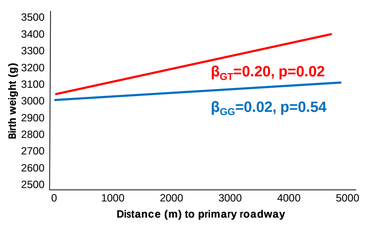
rs2227282 (p=0.008)



rs2243283 (p=0.03)



  - rs2069714 in *INFG* (p=0.04)



DISCUSSION

- We have shown that genetic variation in inflammatory response genes provided evidence for main effects on infant BWT among NHB women in our study and we provide the first evidence that some of these genes interact with air pollution exposure to influence infant BWT.
- Genes in both the pro- (*IL8, IL12A, IL12B, TLR4, CR1, INFG*) and anti-inflammatory (*IL4, IL6, IL10*) cascade were implicated.
- rs17047661 in *CR1* is a missense mutation and has been previously associated with resistance to malaria.
- Replication of these novel interactions will be necessary to confirm that they are real.

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